Synthesis of (±)-Laudanosine and a Study of 1-Benzyl-3-isoquinolone Intermediates

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A keto acid (2) has been converted to tetrahydropapaverine and (±)-laudanosine. Some intermediate 3-isochromanone (**3**) and 3-isoquinolone (**4** and **5**) derivatives have been investigated and structures assigned to these compounds from spectroscopic studies. The 3-isoquinolone tautomer with the *o*-quinonoid structure predominates over the 3-isoquinolinol form, but the analogous oxygen derivative has preferentially a stilbene structure (**3**) with an intact benzene system.

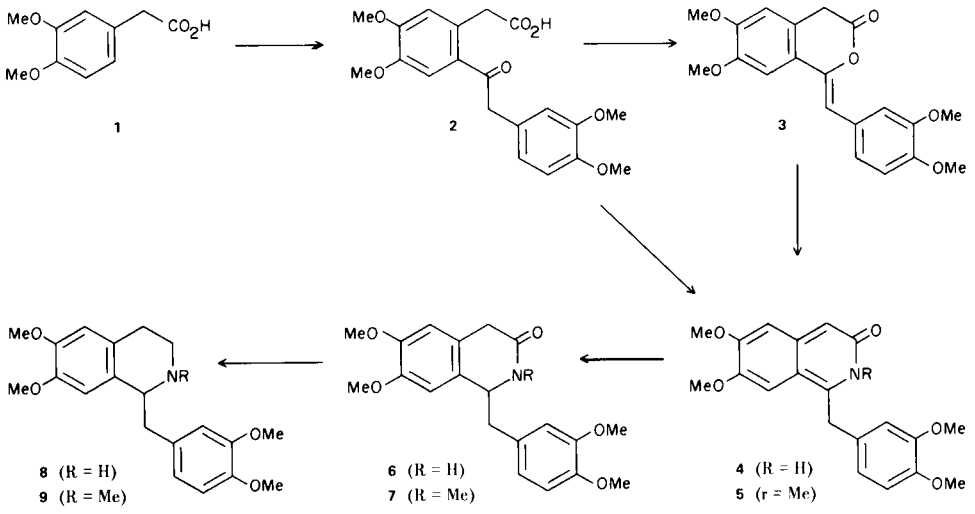
In an earlier communication a new approach was outlined for the synthesis of the several kinds of alkaloids biogenetically derived from compounds of the 1-benzylisoquinoline type (1). The key compound in this projected work was 2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxyphenylacetic acid (**2**) prepared in a simple fashion from an intermolecular acylation of 3,4-dimethoxyphenylacetic acid (**1**) in polyphosphoric acid. From the keto acid (**2**) total syntheses were described for 1,2,3,4-tetrahydropapaverine and (±)-laudanosine. The experimental details for these syntheses are reported in this present article, and in particular the structural formulas of two critical intermediates (**4** and **5**) are revised from the original communication.

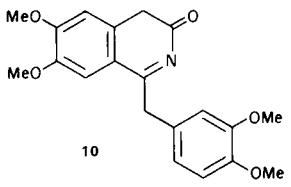
The routes for preparing tetrahydropapaverine (**8**) and laudanosine (**9**) are summarized in Scheme I and the detailed procedures and properties of the intermediates are given in the Experimental section.

3-Isoquinolone Derivatives.

In the original report the compounds **4** and **5** were formulated respectively as **10** and **11**, although both were recognized as examples of the 3-isoquinolone (or 3-isoquinolinol) ring system for which other tautomeric forms are also possible (2). In general, for the 1-benzyl-3-isoquinolone system, at least four prototropic isomers (**12 a-d**) can be considered, and representative compounds with these various tautomeric formulations have been proposed in the literature (3). In the case of an N-H derivative such as **4** all four tautomers (**12 a-d**) are possible, but the *N*-methyl derivative (**5**) can only alternatively be represented as **12 d** ($N\text{-}CH_3$ in place of N-H). For the parent 3-isoquinolone, without the 1-benzyl substituent, the *o*-quinonoid form is principally favored (4); Dewar

SCHEME I





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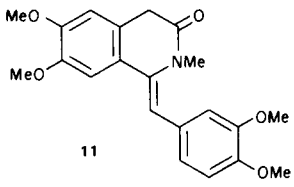

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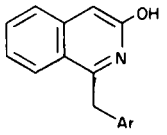
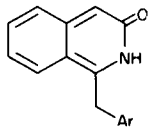


12a



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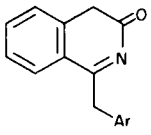
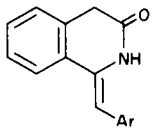
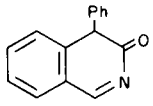


12c



12d



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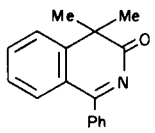

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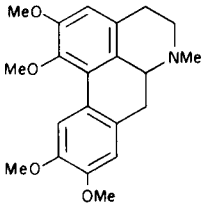

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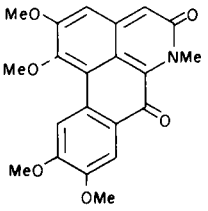

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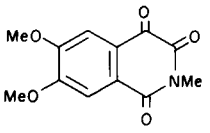

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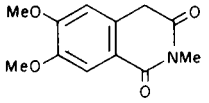

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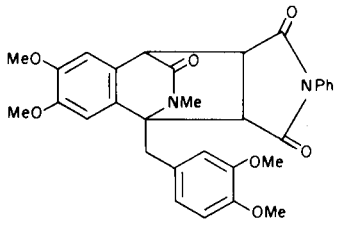

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has calculated the heats of atomization for 3-isoquinolone and 3-isoquinolinol and found that by comparison with other similar benzopyridones (*viz.* isocarbostyril) the difference in energy between the two tautomers is quite small, but 3-isoquinolone is slightly more stable (5). Jones has presented spectroscopic evidence that the equilibrium between the lactam-lactim forms (*cf.* **12a-12b**) is solvent depent (6). Although Smith and co-workers (4) found no support for a structure analogous to **12c**, Gardent and Harmon (7) observed an amide carbonyl absorption band in the infrared spectrum of 4-phenyl-3-isoquinolinol and considered the unsaturated amide (**13**) to be a plausible tautomer. Recently the synthesis of an unambiguous 1,4,4-trisubstituted-3-isoquinolone (**14**) has appeared (8), and this compound provides a good model for electronic spectral comparisons with tautomers of type **12c**.

In general compounds of the 3-isoquinolone series are characterized by high melting points, yellow color and limited solubility in ethanol, ether or benzene. The parent 3-isoquinolone is a weak acid, is readily soluble in aqueous sodium hydroxide and gives a violet color with ferric chloride. In these ways it behaves like a typical phenol, but it also forms a hydrochloride and a picrate. The infrared spectra of several representative members of this ring system show strong absorption bands for an amide carbonyl; there is a broad absorption band in the region of 2700-2500 cm^{-1}, similar to the pattern found by Mason (9) in related pyridones and ascribed by him to

an N-H group of an amide that receives considerable contribution from a dipolar resonance form, but there are no bands in the usual region for either an O-H or N-H group. Compounds **4** and **5** fit these patterns, but most importantly the ultraviolet spectra of the two compounds are very similar, and both exhibit absorption maxima near 404-410 nm. Smith (4) and also Jones (6) found this long wavelength absorption band was characteristic for the lactam or 3-isoquinolone tautomer. Moreover, the electronic spectra of **4** and **5** are distinctly different from those either of structurally related stilbenes or of the isoquinolone, **14**.

The nmr spectrum of **4** is consistent with the assigned constitution. In addition to six aromatic protons there is a singlet at τ = 5.2 for NH and another ascribed to the methylene group at 4.4, with relative areas of the 1 to 2. The four methoxy groups give rise to four separate resonance bands.

In addition to the catalytic hydrogenation of **4** and **5** to afford the tetrahydroisoquinolones (**6** and **7** respectively), the *N*-methyl homolog (**5**) was converted to **7** also by sodium borohydride. By contrast, **4** was unaffected by either sodium borohydride or lithium aluminum hydride; with these reagents there was an apparent reaction with loss of the characteristic yellow color, but probably salts were formed, for the starting compound was recovered on hydrolysis. The original preparation of **4** from the keto acid (**2**) was accomplished with ammonium formate and formic acid under conditions typical for a Leuckart reaction, but none of the expected amino acid or amide (**6**) was obtained, suggesting that the readily formed 3-isoquinolone system was also resistant to reduction by these reagents.

At an early period in this work when the *N*-methyl isoquinolone (**5**) was thought to have the stilbene structure (**11**), the compound was subjected to a photochemical reaction in the attempt to achieve a diaryl coupling and ultimately to synthesize either glaucine (**15**) or the recently discovered alkaloid pontevedrine (**16**) (10). The only crystalline product isolated from the photochemical reactions was 6,7-dimethoxyisoquinolin-1,3,5-trione (**17**). The same compound (**17**) was prepared independently by chromic acid oxidation of 6,7-dimethoxy-2-methyl homophthalimide (**18**) by the method of Mann (11).

A Diels-Alder adduct (**19**) was obtained from a reaction between *N*-phenylmaleimide and **5** in a fashion similar to reactions of other 3-isoquinolones derivatives (12).

3-Isochromanone Derivatives.

A problem of tautomerism similar to that described for 3-isoquinolone can exist in the oxygen analog, but the particular example formed from the keto acid (**2**) by thermal dehydration has the structure of 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone (**3**). The electronic spectrum of **3** is closely similar to 3,3′,4,4′-tetramethoxy-*trans*-stilbene (13). Chemically **3** shows no tendency to react by a Diels-Alder reaction with *N*-phenylmaleimide. Although Holland and Jones have presented evidence that some 3-isochromenones may possess an *o*-quinonoid structure (14) these compounds seem relatively less stable than the corresponding nitrogen compounds.

EXPERIMENTAL

Melting points were taken on a Mel-temp apparatus and are uncorrected. Infrared spectra were determined in paraffin oil mulls on a Perkin-Elmer Model 337 spectrophotometer. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, New York 11377.

[2-(3,4-Dimethoxyphenylacetyl)-4,5-dimethoxyphenyl]acetic acid (**2**).

Powdered 3,4-dimethoxyphenylacetic acid (10 g.) was dispersed in 200 g. of polyphosphoric acid, and the mixture was allowed to stand 24 hours with occasional stirring. A purple color developed within ½ hour and slowly darkened to a red-brown. The syrupy mixture was poured into 1.2 l. of cold water and a pale yellow solid was collected after about 3 hours. The crude product (6.5 g.) was recrystallized from aqueous alcohol to afford the keto acid (**2**), 5 g., m.p. 153-154°; ir bands at 3125, 1715 and 1652 cm^{-1}.

The keto acid (**2**) was alternatively prepared in about the same yield by heating the mixture of 3,4-dimethoxyphenylacetic acid in polyphosphoric acid on a water bath for 20 minutes.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.44; H, 5.98.

1-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone (**3**).

A suspension of 5 g. of the keto acid (**2**) in decalin (150 ml.) was stirred and gradually heated to 190° in an open container to permit the water to escape. The temperature was kept at 190-195° for 30 minutes, and the cooled mixture was diluted with 400 ml. of petroleum ether (b.p. 30-60°), chilled and filtered. The mixed solids of crystals and gum were combined and recrystallized from ethanol as pale golden prismatic crystals, 3 g.; m.p. 165-167°; uv spectrum (in ethanol): λ max (log ϵ) at 326 nm (4.12); ir band for CO at 1754 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66; O, 26.94. Found: C, 67.42; H, 5.51; O, 27.09.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3-isoquinolone (**4**).

A mixture of the keto acid (**2**; 5 g.), ammonium acetate (10 g.) and acetic acid (50 ml.) was slowly heated to boiling and allowed to boil gently for 0.5 hour. The dark brown solution was poured into water (200 ml.), and the crude product (5 g.) had m.p. 216-218°. Recrystallization from chloroform-ligroin gave a yellow solid, m.p. 226-228°; ir band at 1663 for C=O; ir band at 1663 for C=O; λ max in ethanol (log ϵ): 258 (4.77), 288 sh (3.82), 319 (3.55), 366 sh (3.45), 404 nm (3.76).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.95; H, 6.13; N, 4.33.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone (**6**).

A suspension of compound **5** (3 g.) in ethyl acetate (200 ml.) and 1 g. of 10% palladium-on-charcoal catalyst was hydrogenated at an initial pressure of 60 p.s.i. until the uptake of hydrogen

ceased. After the catalyst was removed, the solution was evaporated, and ether was added to the residue. On cooling a granular solid, 1.6 g., m.p. 154-155°, was obtained in two crops. Recrystallization from ethanol gave the amide (**6**) as colorless prisms, m.p. 155-157°; ir bands at 3380 (NH) and 1647 cm^{-1} (C=O).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.57; H, 6.60; N, 4.13.

1,2,3,4-Tetrahydropapaverine (**8**).

A solution of 0.5 g. of 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone (**6**) in 20 ml. of 1*M* borane-tetrahydrofuran was allowed to stand 18 hours, hydrolyzed and boiled for 5 minutes with 10% sodium hydroxide solution. The cooled mixture was extracted with ether, and the ether extract was treated with 2 ml. of ethanol-hydrochloric acid (1:1 V/V). On cooling and scratching there was obtained a colorless solid, 0.1 g., m.p. 212-214°, that was identified as tetrahydropapaverine hydrochloride by direct infrared spectral comparison with an authentic sample (15).

1-(3,4-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-3-isoquinolone (**5**).

A solution of 3.5 g. of the unsaturated lactone (**3**) in ethanol (30 ml.) and 40% aqueous methylamine (25 ml.), obtained by warming the mixture 5 minutes, was allowed to stand 18 hours. After heating on the steam bath 20 minutes, the solution was diluted to 200 ml., cooled and scratched. Yellow needles, 3.1 g., were obtained that melted at 65-68° and showed ir bands for water at 3490 (sharp) and 3360 cm^{-1} (broad). Recrystallization from aqueous acetic acid and rigorous drying *in vacuo* gave a sample, m.p. 156-158°, whose m.p. varied with rate of heating; ir band at 1675 cm^{-1} (C=O); λ max in ethanol (log ε) at 258 (4.95), 290 sh (4.14), 308 (3.69), 319 (3.67), 410 nm (3.85).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.18; H, 6.14; N, 3.68.

1-(3,4-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone (**7**).

(a) By Catalytic Reduction of **5**.

The *N*-methyl-3-isoquinolone (**5**; 2 g.) was hydrogenated in ethanol solution with platinic oxide catalyst (0.2 g.), with the uptake of hydrogen virtually complete within 20 minutes. The filtered solution was concentrated and on cooling slowly deposited 1.2 g. of a colorless crystalline product, m.p. 146-148°. Recrystallization from aqueous ethanol gave an analytical sample, m.p. 148-149°.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77; O, 21.54. Found: C, 67.83; H, 6.78; N, 3.97; O, 21.84.

(b) By Sodium Borohydride Reduction of **5**.

To a sample of the 3-isoquinolone derivative (**5**; 0.4 g.) dissolved in ethanol (15 ml.) was added sodium borohydride (0.2 g.). The yellow color faded slightly and after diluting with water, heating to boiling and allowing to cool the solution deposited 0.3 g. of yellowish crystals (m.p. 146-148°) in two crops. The infrared spectra and mixture m.p. (undepressed) showed this product was identical with the compound from catalytic hydrogenation of **5**.

(±)-Laudanosine (**9**).

To 80 mg. of compound **7** was added 8 ml. of 1.0 *M* solution of borane-tetrahydrofuran. The solid dissolved in 10 minutes and the solution was allowed to stand 2 hours, hydrolyzed with 5% sodium hydroxide and cooled. A colorless solid (30 mg.; m.p. 113-114°) was collected. The product was identical with (±)-laudanosine (16) by infrared spectral comparison.

Photolysis of 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-3-isoquinolone.

A solution of the isoquinolone (2.3 g.) in *t*-butyl alcohol (250 ml.) and benzene (60 ml.) was irradiated for 6 hours in a Rayonet reactor equipped with 2735 Å-tubes. A yellow solid (0.4 g., 276-278°) was deposited on the walls of the reaction vessel. Additional product (0.1 g.) was obtained from the concentrated solution. For analysis the sample was recrystallized from dimethylformamide-ethanol (1:2 v/v; 60 ml.) as a yellow powder, m.p. 280-281°; infrared bands at 1680, 1710 and 1735 cm^{-1}; mass spectrum (parent ion) 249.

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62 (M.W. 249). Found: C, 57.77; H, 4.28; N, 5.91.

N-Methyl-6,7-dimethoxy-1,3-isoquinolinedione.

4,5-Dimethoxyhomophthalic acid (**18**; 3 g.) was dissolved in 40% methylamine solution (8 ml.), and after 0.5 hour the excess methylamine was stripped off under reduced pressure. The residual solution was covered with decalin (75 ml.) and gradually heated (0.5 hour) to 195° with stirring in an open container. The cooled reaction mixture was diluted with 100 ml. of petroleum ether (b.p. 30-60°) and a burnt orange solid (2.8 g.) was collected and washed with more petroleum ether. The homophthalimide was recrystallized from aqueous acetic acid as yellowish-green needles, m.p. 213-215°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; O, 27.21. Found: C, 61.02; H, 5.57; N, 6.00; O, 27.38.

1,3,4-Trioxo-2-methyl-6,7-dimethoxyisoquinoline.

A suspension of *N*-methyl-6,7-dimethoxy-1,3-isoquinolinedione (0.5 g.) in warm 60% sulfuric acid (20 ml.) was treated with a saturated solution of potassium dichromate (2 g.). After the reaction subsided the mixture was heated to boiling over a 20 minute period. The cooled mixture was filtered and washed four times with water to leave a bright yellow solid of the triketone, 0.35 g. m.p. 278-280°. This product was identical with the photolytic triketone by infrared spectral comparison.

Diels-Alder Reaction of 3-Oxolaudanosine with *N*-Phenylmaleimide.

To a solution of *N*-phenylmaleimide (0.5 g.) in ethyl acetate (20 ml.) was added a filtered solution of 3-oxolaudanosine (**7**; 0.9 g.) in ethyl acetate (30 ml.). The reaction mixture was warmed 2 minutes, allowed to stand 24 hours, heated and diluted to near turbidity with petroleum ether (b.p. 30-60°). On cooling a pale yellow solid (0.6 g., m.p. 230-231°) precipitated. On recrystallization from ethanol, colorless prismatic crystals, m.p. 234-235° were obtained.

Anal. Calcd. for $C_{31}H_{30}N_2O_7$: C, 68.62; H, 5.57; N, 5.16. Found: C, 68.45; H, 5.58; N, 5.28.

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